Synthesis of Novel Tetraazamacrocyclic Bisquinoline Derivatives as Potential Antimalarial Agents

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Abstract: Novel bisquinoline derivatives of tetraazamacrocyclic compounds, namely 4,10-bis(7-chloroquinoline)-1,4,7,10-tetraazacyclodecane (1, Scheme 1); 4,10-bis(7-chloroquinoline)-1,7-dimethyl-1,4,7,10-tetraazacyclodecane (6, Scheme 2); 4,11-bis(7-chloroquinoline)-1,4,8,11-tetraazacyclotetradecane (6a, Scheme 3) and 4,10-bis(7-chloroquinoline)-1,4,7,10-tetraazacyclohexadecane (5, Scheme 2) which are potential antimalarial drugs have been synthesized. The macrocyclic framework had to be modified to allow attachment of the substituent (4,7-dichloroquinoline) at the nitrogen atom. The initial synthesis of (1) by direct derivatization was inefficient for selective functionalization and consequently the desired product was isolated in low yield. We have found that by choosing N-methylpyrrolidinidine as the reaction solvent, with triethylamine as base, and elevating the reaction temperature, product (1) was accessed with yields of up to 45%. Compounds 6, 6a and 6b were synthesized via regioselective modification of the macrocyclic framework before the attachment of the 4,7-dichloroquinoline substituent.

Keywords: Aromatic nucleophilic substitution, Bisquinoline, cyclam, cyclen, tetraazamacrocyclic.

INTRODUCTION

Tetraazamacrocyclic compounds and their synthetic analogs featuring the tetraazamacrocyclic structural motif have been extensively documented as having a wide variety of properties in biological and medical studies. Recent applications of the structural motifs of these macrocycles, particularly, 1,4,7,10-tetraazacyclodecane, (cyclen), have been limited to a variety of diagnostic and therapeutic pharmaceutical agents and for the development of magnetic resonance imaging contrast agents. In the same vein, 1,4,8,11-tetraazacyclotetradecane, (cyclam), is an important structural moiety for the development of (i) selective sensors for adenosine triphosphate, zinc and nitric oxide regulation/delivering processes (ii) radionuclidic chelates for diagnosis and treatment and (iii) CXCR4 Antagonists [1, 2].

The structural resemblance between tetraazamacrocycles (e.g. cyclen) and hemes [1] as well as their ability to bind to metal ions [1], has prompted us to take advantage of these unique properties to design novel antimalarial agents. The tetraazamacrocycles were incorporated into quinolines to be used for antimalarial chemotherapy to augment the efficacy of chloroquine against drug-sensitive and -resistant strains of malarial parasites [1]. Chloroquine exerts a toxic effect on malarial parasites by preventing hemoglobin formation from heme. Thus, free heme accumulates in the food vacuole and generates reactive oxygen species causing lysis of membranes and inhibits many other processes. Since it has been well documented that the 4-aminoquinoline or its derivatives, especially those with the 7-chlorine atom, possess a marked antimalarial activity and cyclen is structurally similar to heme [1], we were encouraged to develop these tetraazamacrocyclic based bisquinoline antimalarial agents. With this idea in mind, and based on the additivity principle in candidate drug design, we envision that the molecular combination of the 7-chloroquinoline moiety (as in Chloroquine) with the tetraazamacrocyle (e.g. cyclen) may be of merit in antimalarial chemotherapy [1].

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The quinoline nucleus occurs in many natural compounds as the cinchona alkaloid and it is a pharmacologically active substance which displays a broad array of biological activity [3, 4]. For this reason, the quinoline scaffold is considered as one of the most important ingredients in drug discovery research. The biological activity in quinoline exhibits antiasthmatic [5], antibacterial [6], anti-inflammatory [7], antihypertensive [8] and antimalarial [9] properties and therefore quinoline derivatives can be used for a wide variety of chemotherapies; for instance as antimalarial agents such as chloroquine and its congeners [10-12].

With the emergence of chloroquine resistance, there has been an urgent need to develop a new antimalarial drug with superior pharmaceutical benefits to effectively combat the disease [13, 14]. In the past two decades, a number of potent 4-aminoquinoline-based drugs that overcome chloroquine resistance have been reported [12, 15]. Most of them contain the 7-chloroquinoline nucleus of chloroquine and vary in the length and nature of their basic amine side arm [16]. In this investigation, we are reporting a general method of synthesis of tetraazamacrocyclic bisquinolines featuring the 7-chloroquinoline structural motif that displays antimalarial properties. With modifications to the synthetic methodology developed by Vennstrom et al. [17], we developed an efficient route to preparing cyclen- and cyclam-based bisquinoline analogs of chloroquine. These tetraazamacrocyclic derivatives were prepared by incorporating the macrocyclic moiety, for instance the cyclen, into the 4,7-dichloroquinoline through coupling reactions to generate a series of analogs, which could be used for antimalarial chemotherapy in order to augment the efficacy of chloroquine against drug-susceptible and resistant strains of malarial parasites.

The N-functionalization of tetraazamacrocycles, for example, cyclen has been extensively studied [18] due to its diverse medicinal and pharmaceutical applications. However, the application of these compounds, especially the cyclen and cyclam [19] derivatives, in biological and medicinal studies [20] have been severely limited by lack of efficient synthetic methods for selective functionalization of these tetraazamacrocyclic compounds [21]. Generally, derivatization of these compounds is accomplished through N-derivatization which could be achieved in two ways: by direct derivatization-
Synthesis of Tetrazamacrocyclic Bisquinoline Derivatives

Scheme 1. Reagents and conditions: (i) Et3N, NMP/180-200 °C, 4 h; (ii) K2CO3, DMF/140 °C, 24 h.

Scheme 2. Reagents and conditions: (i) 40%aq. glyoxal, dry MeCN, 55-58 °C; (ii) excess Mel, dry MeCN, rt, 3 days; (iii) NaOH, H2O, reflux, 48 h; (iv) 4,7-dichloroquinoline, dry NMP, Et3N, 260 °C, 4 h.

RESULTS AND DISCUSSION

N-functionalization of tetrazamacrocycles or their derivatives have been accomplished by employing two approaches: direct derivatization and protection-derivatization-deprotection. Using both approaches, we have successfully synthesized three new cyclen and cyclam derivatives: 4,10-bis(7-chloroquinoline)-1,7-dimethyl-1,4,7,10-tetraazacyclodecane (6, Scheme 2), 4,11-bis(7-chloroquinoline)-1,4,8,11-tetraazacyclotetradecane (6a, Scheme 3) and 4,16-bis(7-chloroquinoline)-1,4,7,10-tetraazacyclotetradecane (6b, Scheme 3) which are potential antimalarial agents. Using a regioselective approach, the precursors for compounds 6, 6a, and 6b, were successively obtained using the protection-derivatization-deprotection approach prior to their respective conversions to the desired bisquinolines, while direct derivatization approach was employed to obtain 4,10-bis(7-chloroquinoline)-1,4,7,10-tetraazacyclodecane (1, Scheme 1). Through extensive literature review, we found out that only a couple of synthetic methods had been previously reported [1, 22] for the preparation of cyclen and/or cyclam bisquinoline derivatives in which a bulky aromatic substituent such as quinoline bonds directly to the macrocycle framework via the C-N bond. Most of the synthetic applications involving the syntheses of these bulky tetrazamacrocyclic derivatives usually involved attachment of the requisite substituent via methylene carbons [23, 27]. Coupling reactions involving the aliphatic diaminoketones or cyclo polyamines with bulky aromatic nuclei, such as quinoline, via C-N bond is more common and is extensively documented. [17, 18, 26] Khan et al. [1] and Girault et al. respectively reported cyclen [1] and cyclam [22] bisquinoline derivatives in which the bulky quinoline moiety directly attached to the tetrazamacrocycle without a methylene carbon linkage. Khan et al. [1] utilized DMF as solvent with potassium carbonate as base, and after a tedious purification process isolated the cyclen bisquinoline with a 35% yield. To the best of our knowledge, there has not been any synthetic report on the ethylene (C2H4CH2-) cross-bridged cyclam and cyclen [24, 25] bisquinolines analogs. However, the synthesis of the cyclam bisquinoline analog without the cross-bridge had been carried out by Girault et al. [22] using the same procedure as that used by Khan et al. [1] (shown in route 2 of Scheme 1).

Direct Derivatization

A number of methods were investigated while pursuing optimal conditions for the synthesis involving the direct derivatization pathway, particularly, for the synthesis of compounds (1). Eventually, the route which allowed for the easiest and most efficient purification was adopted by modifying the method of Vennerstrom et al. [17]. However, in applying the direct derivatization method, even though Khan et al. [1] successfully isolated (1), the yield was 35%. Because this method involves coupling of the 4,7-dichloroquinoline directly to the tetrazamacrocyclic ligand, steric
hindrance may limit the formation of the expected product and consequently the yield is low.

In this report, we have employed a modification to the method used by Vennerstrøm et al. [17] using N-methylpyrrolidinone (NMP) as solvent and anhydrous triethylamine as the base at an elevated temperature of 180-200 °C to isolate these target cyclo- or cyclam bisquinoline analogs. Precipitation of the crude product from the reaction mixture by addition of iced cold water and subsequent purification by recrystallization from the appropriate solvent or by column chromatography resulted in improved yields. Using this synthetic route, triethyl amine salt (Et3N-N) consistently precipitates out from the crude reaction mixture when the reaction mixture is allowed to cool to room temperature within 48-72 h. The formation of the triethylamine salt (Et3N-N), which is filtered out as an impurity during the workup is an indication of the shift of the reaction equilibrium to the product side, resulting in substantial formation of the product reflected in the improved yield. Upon repeating the reactions multiple times, we found that the formation of the triethylamine salt was consistent, hence it was used as a confirmation of the occurrence of the reaction, particularly for the synthesis on cyclo- and cyclam bisquinolines respectively. The bisquinoline products isolated in this fashion, particularly the cyclam analog (1), is not only relatively higher yielding but also purer (>98% pure) since the crude product is easily purified from ethanol. The alternative pathway, however, involves multiple column purifications on silica gel using eluents of varying ratios of CH3Cl/MeOH/NH4OH. This makes the purification very laborious and time consuming. It is worth noting however, that while (1) was easily isolated in moderate yields by precipitation with cold water, the relatively more hydrophobic alkyl substituted analog (6) could not be precipitated from water. It is only upon addition of water/ether in 1:1 ratio and cooling at 4 °C for two or three days before the product precipitates. For compound (4) and the cyclam analog (not reported here), the successful outcome of their synthesis critically depends on the precipitation of triethyl amine salt from the reaction mixture after the reaction. Generally, compound (4) (Scheme 1, method i) is easily purified by recrystallization and the yields ranged from 40-45% due to variability in handling of the crude reaction mixture during workup and/or the crude product during the purification process. On the other hand, purification of the cyclam bisquinoline analog is relatively difficult due to challenges encountered in finding the appropriate recrystallization solvent. Therefore, it becomes necessary to purify it by column chromatography (gravity) using silica gel and a solvent system of CH3Cl/MeOH/NH4OH in 4:0.2:0.1 ratio.

Protection-Derivatization-Deprotection

The ligands 1,7-dimethyl-1,4,7,10-tetraazacyclododecane (5), 1,4,8,11-tetrazacyclotetradecane (5a) and 1,4,7,10-tetraazacyclononane (5b) which were converted to the targeted bisquinolines (6), (6a), and (6b) respectively were prepared using the protection-derivatization-deprotection method which is extensively documented in the literature. [24, 25] Precursor (5) was synthesized using a modification of the literature procedure [27] while precursors (5a), and (5b) were prepared from cyclo- and cyclam respectively in a similar manner according to the Weisman procedure [25]. Compounds (5) and (5b), from cyclo- and compound (5a) from cyclam, were all prepared in four steps. (5) was accessed via amination of the secondary amines of the macrocyclic polyamine followed by symmetrical N,N'-diacylation and subsequently by alkaline hydrolysis. (5a) and (5b) were accessed via amination of the secondary amines of the macrocyclic polyamine and symmetrical N,N'-dibenzyl cross-bridged cyclam or cyclam, followed by reduction with NaBH4 in ethanol and dehydroxylation by catalytic hydrogenolysis (1 atm. H2, 10% Pd/C, HOAc). To access the target bisquinolines (6), (6a), and (6b), a combination of features of various literature procedures for reactions involving a variety of diaminoalkanes and/or linear polyaminoalkanes with 4-halo-7-chloroquinoline derivatives [17, 18, 20] were taken and modified to suit the synthesis for the conversion of the precursors (5), (5a) and (5b) to the desired bisquinolines: (6), (6a) and (6b) respectively. The syntheses of these bisquinolines is by aromatic nucleophilic substitution on 4,7-dichloroquinoline [17].

EXPERIMENTAL

General Information

All reactions were performed in anhydrous solvents under inert atmosphere, unless otherwise indicated. Anhydrous solvents, 1-methyl-2-pyrrolidinone (NMP), acetonitrile and DMF, as well as all other reagents, were used as received from a commercial source. Reactions were monitored using thin layer chromatography (TLC) on 200 μm Sorbent Technologies silica gel plates and visualized under UV light. Column chromatography was performed using Sorbent Technologies gravity silica gel (60 Å pore size, 63-200 μm, 65 x 250 μm). LC-MS was obtained using Shimadzu LCMS-2020 1:1 methanol/water mixture. 1H and 13C NMR spectra were recorded at 300 MHz and 75 MHz on Bruker Avance II 300 spectrometer in either CDCl3 or D2O with TMS or TSP respectively, as internal standard. 1H NMR spectral data are reported as follows: chemical shift (δ, ppm) (multiplicity, coupling constants, number of hydrogens). Multiplicity is designated as: s, singlet; d, doublet; t, triplet; q, quartet; quint; m, multiplet; br, broad; dd, doublet of doublets; dt, doublet of triplets; td, triplet of doublets. High resolution mass spectral (HRMS) data was obtained at the Mass Spectral facility at the Department of Chemistry and Biochemistry at the University of Arizona, Tucson Arizona.

Synthesis of cis-Decahydro-2a,4a,6a,8a-tetraazacyclononane-1,7-diamine (9)

To a stirred suspension of cyclo- (5.003 g, 29.04 mmol) in anhydrous acetonitrile (20 mL) was added 40 wt% aqueous glyoxal
Synthesis of Tetraazaamacryloyl Bisquinoline Derivatives

Current Organic Synthesis, 2014, Vol. 11, No. 6 198

(3.2 mL, 68.92 mmol) in drops within a period of 15 min, during which time the mixture became colorless. The reaction mixture was heated at 55-58 °C with stirring for 2 h. After the reaction mixture was cooled to room temperature, the excess solvent was removed under reduced pressure to give a dark-brown viscous oil which was dissolved in distilled water (15 mL) and extracted with methylene chloride (15 mL x 10). The combined extract was dried over anhydrous MgSO₄, filtered, and the CH₂Cl₂ was removed under reduced pressure to give a moist white solid, which was lyophilized to give a solid white product (1) (5.336 g, 93%). ¹H NMR (300 MHz, CDCl₃): δ 1.21 (s, 2 H), 3.09-2.91 (m, 8 H), 2.81-2.63 (s, br, 4 H), 2.63-2.49 (m, 4 H); ¹³C NMR (75 MHz, CDCl₃): δ 78.1 (N(CH₃)), 50.7 (CH₂N), LC-MS (ESI) m/z: 195.6

Synthesis of cis-Decahydropyrrolo[3,2-b]pyrrole (3a)

To a stirred suspension of cyclohexanone (0.5003 g, 24.97 mmol) in anhydrous acetonitrile (41 mL) was added 40 wt % aqueous glyoxal (421 μL, 9.025 mmol) in drops over a period of 1 h while stirring at room temperature. The reaction mixture was heated at 60 °C with stirring for 4 h. The reaction mixture was cooled to room temperature, the excess solvent was removed under reduced pressure to give a viscous oil which was dissolved in CH₂Cl₂ (1 mL) and passed through a column packed with amonia oxide, using 1% methanol in methylene chloride (150 mL) as an eluent at a flow rate of 2 drops/min. The excess solvent in the eluted compound was removed under reduced pressure to give a colorless oil product which was lyophilized to give a white solid product 3a (0.5451 g, 98%). ¹H NMR (300 MHz, D₂O): δ 5.33 (t, J = 10.7 Hz, 2 H), 3.08 (s, 2 H), 2.94 (s, 6 H), 2.74 (d, J = 11.6 Hz, 2 H), 2.40-1.97 (m, 8 H), 1.22 (d, J = 13.2 Hz, 2 H); ¹³C NMR (75 MHz, CDCl₃): δ 56.1 (CH₃), 34.4 (CH₃O), 25.3 (CH₃), 44.8 (CH₃), 19.6 (CH₂C₆H₄); LC-MS (ESI) m/z: 223.

Synthesis of 1,7-dimethylgloxal Cyclodimide Salts (4a)

To a solution of 3 (1.339 g, 6.894 mmol) in anhydrous acetonitrile (100 mL) was added methyl iodide (3.3 mL, 53.48 mmol) in one portion. The reaction mixture was stirred under nitrogen at room temperature for 72 h during which time the product precipitated as a white solid. The resulting white solid was collected by suction filtration and washed with CH₂CN (15 mL) followed by ether (15 mL) and then dried in vacuo to give a white solid product (1.3749 g, 97%). ¹H NMR (300 MHz, D₂O): δ 7.43-7.84 (m, 10 H), 5.28 (d, J = 13.0 Hz, 2 H), 5.08 (s, 2H), 4.71 (s, 2 H), 4.51-4.35 (t, J = 21.6, 4.3, H, 2 H), 3.813-6.65 (d, J = 22.6, 5.4, Hz, 2 H), 3.6-2.4 (m, 4 H), 3.21 (d, J = 13.0 Hz, 4 H); ¹³C NMR (75 MHz, CDCl₃): δ 179.8, 146.1, 146.7, 51.2, 60.5, 62.3, 76.8, 90.9, 124.6, 129.5, 131.4, 133.1.

Synthesis of 1,7-dimethylgloxal Cyclodimide Salts (4b)

To a solution of (3b) (0.6669 g, 4.462 mmol) in anhydrous acetonitrile (25 mL) was added in one portion benzyl bromide (4.3 mL, 36.1815 mmol). The resulting reaction mixture was stirred under nitrogen for 7 days. The precipitate that formed was collected by suction filtration, washed with MeCN (5 mL) and then dried in vacuo to give a white solid (1.3749 g, 97%). ¹H NMR (300 MHz, D₂O): δ 7.43-7.84 (m, 10 H), 5.28 (d, J = 13.0 Hz, 2 H), 5.08 (s, 2H), 4.71 (s, 2 H), 4.51-4.35 (t, J = 21.6, 4.3, H, 2 H), 3.813-6.65 (d, J = 22.6, 5.4, Hz, 2 H), 3.6-2.4 (m, 4 H), 3.21 (d, J = 13.0 Hz, 4 H); ¹³C NMR (75 MHz, CDCl₃): δ 179.8, 146.1, 146.7, 51.2, 60.5, 62.3, 76.8, 90.9, 124.6, 129.5, 131.4, 133.1.
cis-aminal. This compound was then either converted to the symmetrically protected N,N'-dialkyl aminal bridged salt, followed by alkaline hydrolysis to afford the N,N'-dialkyl cyclic, or the symmetrically protected N,N'-dibenzy1 aminal bridged salt followed by reduction and debenzylation by catalytic hydrogenolysis to obtain the ethylene cross-bridged macrocycle. These tetraazaacrocycles were then coupled to 4,7-dichloroquinoline via nucleophilic aromatic substitution to access the target bisquinolines. Despite the challenges encountered during the synthetic process of attaching the 4,7-dichloroquinoline to the tetraazaacrocyclic molecules in the final stage, the bisquinolines were prepared with overall yields of 15-25% for compounds (4) (Scheme 4). Even though the individual yields of the intermediate products were all high (85-95%) in the first four step reaction sequences.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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